Brit. J. Psychiat. (1965), 111, 511–516

The Management of Depression in Hospital

A Comparative Trial of Desipramine and Imipramine

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Introduction

Desipramine (Pertofran) is a metabolite of imipramine (Tofranil) originally isolated by Herrmann, Schindler and Pulver (1959) and found to be identical with the synthetic compound G.35025. Animal experiments (Gillette *et al.*, 1961) suggest a more rapid action for desipramine, and the majority of clinical trials to date confirm this impression for humans (e.g. Kline *et al.*, 1962; Krakowski, 1963). Some controlled trials, however, (Azima *et al.*, 1962; Hollister *et al.*, 1963) fail to establish that desipramine is either faster acting or more effective than imipramine.

Whilst attempting to establish a rationale for the use of these drugs on in-patient depressives, the present study compares desipramine with imipramine, under controlled conditions, for (1) anti-depressant activity, (2) speed of action and (3) presence of side-effects.

Population

All patients entering the trial were female, admitted during the period November, 1963 to March, 1964, inclusive.

In this time 109 patients were admitted to the acute short-stay ward. Of these 92 were diagnosed as suffering from depressive illness uncomplicated by organic brain disease or schizophrenic symptoms. The diagnosis was made by each author independently and in many cases by a third psychiatrist. There were 19 patients so acutely ill as to require immediate electroplexy. A pilot trial was carried out on 8 patients to test procedure and establish dosage levels. One patient improved very rapidly and was unrateable, and 6 discharged themselves before commencing therapy. Two left hospital a few days after starting tablets, whilst three were withdrawn because of rapid deterioration and given electroplexy. It was not felt that these patients should be included in the results because of the shortness of the period they were on drugs.

The remaining 53 patients completed the full three-week trial period. Their ages ranged from 14 to 79, with a mean of 51·3. There were 18 with one or more previous admissions, and an additional 9 had had out-patient management for depression at one time or another. Thirty-nine had living spouses; the remainder were either single, widowed or divorced. Using orthodox clinical methods of diagnosis, 29 patients were classified as suffering from endogenous depression and 24 from reactive depression. Using the Hamilton Rating Scale for depression (Hamilton, 1960), scores ranged from 28 to 70, with a mean of 43·6. We consider this to be a more useful method of description and comparison because of the unreliability of clinical diagnosis (Wilson *et al.*, 1964; Martin, 1963).

Method

Following admission patients were left for 3 to 14 days without medication except for night sedation; the longer periods were for those who had had anti-depressant drugs immediately prior to admission. During this phase various investigations were carried out, a complete social history obtained from the next-of-kin by a psychiatric social worker and a full clinical history taken by the clinician. Patients then entered the double-blind trial for a period of three weeks. At the end of the three-week period they were disposed of in one of three ways: (1) those showing marked improvement (approximately 80–100 per cent. improvement, Hamilton scale) were discharged on a maintenance dose of the appropriate drug, (2) those

with moderate improvement (approximately 40–80 per cent. improvement, Hamilton scale) were, with two exceptions, continued on the blind trial for a further two weeks and (3) those showing little or no improvement (0–40 per cent.) were given alternative treatment, usually electroplexy.

Rating

Ratings on the Hamilton Rating Scale were performed immediately before the commencement of the trial and at weekly intervals thereafter. The authors rated independently after separate interviews and achieved a high correlation (r=0·89) between scores.

Dosage Schedules

It was considered desirable to achieve maximum dosage rapidly, and experience in the small pilot trial showed that there were no serious drawbacks to this technique. Patients were given 25 mg. of the drug t.i.d. initially and this was increased to 75 mg. t.i.d. after three days. The higher dose was continued throughout the trial unless serious side-effects occurred. Tablets were identical in size, shape and colour and were administered randomly by the Chief Pharmacist, The code was broken for each patient as she finished the trial. Hypnotics were prescribed at night where necessary.

Investigations

Weekly blood and urine analysis was performed. Liver function tests (bromsulphthalein) were done at the beginning and end of the trial. Electrocardiographs were taken immediately pre-trial and at weekly intervals throughout.

Side-effects

A list of 22 possible side-effects was obtained from the literature on both drugs. Because many of these could be confused with symptoms, the check-list was examined before trial to help subsequent evaluation.

Results

1. Controlled Trial

Anti-depressant Activity

Table I illustrates the distribution of cases on a percentage scale calculated from the drop at the end of three weeks on the pre-trial raw scores. This shows a slight trend in favour of imipramine in the top 20 per cent. (those symptom-free or almost so). However this does not reach statistical significance.

Table I

Distribution of Cases on the Basis of Percentage Improvement on Hamilton Scores After Three Weeks

% Improvement	Imipramine	Desipramine
100	15	10
90	2 (62%)	3 (50%)
80		
70	0	3
60	4	3
50	1	1
40	0	0
30	1	2
20	1	0
10	1	0
0	2	4
	N=27	N=26

Further analysis was carried out to determine whether the initial severity of the illness influenced the results. This was done (Table II) by grouping patients according to their initial raw scores on the Hamilton scale and working out the mean percentage improvement for each

Table II

Average Percentage Improvement After Three Weeks for Different Categories of Initial Severity

Initial Raw Score (H.S.)	Average % Improvement		Kendal S + when desipramine is better
	Imipramine	Desipramine	
Up to 34 ..	75	99	−18
35 to 44 ..	51	65	− 4
45 to 54 ..	83	80	+10
55+	66	54	+19
			+ 7

The total value of S is +7 and this had approximate expected variance of 676, indicating that values of S of this magnitude or less would occur by chance 80 per cent. of the time.

group at the end of three weeks. Statistical analysis (using Kendal's S) shows that there is no significant difference between the drugs in this respect, though there is a slight tendency for the less severely ill to do better on desipramine and the more severely ill better on imipramine.

Speed of Action of the Drugs

We measured speed of activity by estimating the percentage improvement on the initial raw score on the Hamilton scale at the end of one week of therapy. Because of the possibility that milder forms of depression may show a quick response to environmental factors we used a matching procedure on the basis of the initial scores. This was done to within 3 points of difference on the scale. The 30 cases so obtained (15 on imipramine and 15 on desipramine) were also reasonably matched with regard to four other clinical items found to be related to good prognosis in subsequent analysis (Table V). The mean percentage improvement after one week with these cases was 50 per cent. for imipramine and 35 per cent. for desipramine. Whilst the trend is in favour of imipramine this is not significant ($\chi^2=1\cdot6$, $p<0\cdot05$).

Side-effects

There appears to be little difference between the two drugs as regards the frequency or nature of their side-effects (Table III). In most patients these were trivial and evanescent, but two elderly patients on imipramine had syncopal attacks and required reduction of dosage. Two patients developed rashes. One responded to anti-histamines and the other disappeared spontaneously. One patient developed mouth ulcers which were considered to be attributable to drug-induced dryness. The patient insisted on continuing tablets despite this.

Liver function: Six patients showed abnormal retention of bromsulphthalein before the trial. One had a level of 54 per cent. (normal =0–5 per cent.) but had negative results on a battery of liver function tests. She refused electroplexy and was included in the trial. After three weeks on imipramine her retention was reduced to 12 per cent. The other five patients (4, desipramine, 1 imipramine) had retention of from 19 to 21 per cent. before trial. Three of these returned to normal and two remained unchanged at the end of three weeks. Of those with a normal pre-trial test, 2 patients showed abnormal retention at the end (22 per cent. and 36 per cent.). Both patients were on imipramine and two weeks after cessation of the drug the test returned to normal.

TABLE III
Frequency of Side-effects for Both Drugs

	Imipramine	Desipramine
Dry mouth	8	6
Blurred vision	4	4
Sweating	5	5
Tremor	2	4
Syncopal attacks	2	0
Rash	1	1
Headache	1	1
Palpitation	1	0
Dizziness	2	3
Flushing	2	0
Constipation	2	4
Overactivity	0	1
Anxiety	1	0
Nausea	0	1
General weakness	0	1
Tinnitus	2	1

None of the patients described above showed clinical jaundice at any time and as the bromsulphthalein test is highly sensitive the interpretation of these findings is difficult.

Blood and urine analysis remained normal in all cases throughout.

Electrocardiographs were recorded to investigate the findings of other workers (Schou, 1962; Kristiansen, 1961) that changes can occur, particularly in the T waves, in patients on imipramine and desipramine. The detailed findings in the present investigation will be reported elsewhere. Definite changes were seen in the records of 13 (24 per cent.) patients (7 on imipramine, 6 on desipramine). These were one or more of the following changes: flattening or inversion of the T waves in the standard leads, extrasystoles and persistent tachycardia. The interpretation of the changes is a difficult matter but they were not accompanied by overt cardiac distress of any kind.

2. COMBINED ANALYSIS

In view of the fact that these two drugs are chemically closely related and in this trial

have been demonstrated to be closely related in their clinical effects, we have treated them as a unit in all subsequent analyses.

Table IV illustrates the outcome and disposal after three weeks in hospital. It is interesting to note that 8 of the 13 patients in the moderately improved category, who were extended to five weeks on drugs, reached the marked improved category and were discharged.

TABLE IV

Disposal After Three Weeks

Recovered ..	26	Discharged.
	3	Not discharged for social reasons.
Moderately improved ..	13	Trial extended for 2 weeks After this 8 recovered and were discharged, 5 did not benefit and received alternative treatment.
Little or no change ..	10	Given electroplexy.
	1	Other treatment.
	N=53	

Table V lists the factors in the patient's pre-trial presentation which were found to be significantly associated with good outcome on drugs. Table VI shows the high predictive value of changes in the Hamilton scale scoring after one week. N in this table is only 52, as one of the patients was inadvertently not rated at the one-week stage.

TABLE V

Pre-treatment Factors Significantly Associated with Good Prognosis

Score under 50, Hamilton scale ..	p ·01
No previous admission	p ·01
Good concentration	p ·02
No impairment of work .. .. .. (Item 7 Hamilton scale)	p ·02

The scores for the individual symptoms on the rating scale were examined critically after one week to detect any extreme differences or similarities between those who ultimately showed marked improvement and those who did not. Most of the patients who eventually responded to the drugs showed dramatic improvement in the first week on items (1) depressed mood, (7) work and activities and (10) anxiety (psychic). On the other hand the majority of patients, irrespective of outcome, showed noticeable improvement in the following items: (3) suicide, (9) agitation and (17) loss of weight.

TABLE VI

Prediction of 3-Week Outcome from the Percentage Improvement on Hamilton Scale After One Week of Therapy

	Marked Improvement	Others	Total
Less than 50% improvement after 1 week	6	21	27
More than 50% improvement after 1 week	22	3	25
Totals	28	24	52

Highly significant result: χ^2 25·8, $p<\cdot001$.

Three-month Follow-up

Of the 29 patients who had shown a marked response to drugs in three weeks, 22 (75 per cent.) have been seen three months after completing the trial. All were on maintenance doses (13 on imipramine, 9 on desipramine). The thirteen on imipramine remained symptomless, but one patient on desipramine had relapsed and been re-admitted.

DISCUSSION

1. *The Controlled Trial*

Our results do not suggest that desipramine is in any way superior in the treatment of in-patients suffering from depression. Imipramine, in fact, showed itself slightly better in its overall anti-depressant effect, but not significantly so. Examining the degree of improvement at the end of one week did not confirm the prediction made from animal experiments that desipramine would act faster. Imipramine again was somewhat better but the result did not reach statistical significance.

Our findings are in agreement with those of Wilson *et al.* (1964) who conducted a controlled trial closely resembling ours. We do not consider, however, that it is possible to draw valid comparisons with other studies (e.g. Ban and Lehmann, 1962) because the populations treated are very different from ours and many of the trials are uncontrolled.

2. *The Use of Drugs on In-patient Depressives*

We agree with Spear *et al.* (1964), that an anti-depressant drug which does not get the patient better within three weeks has limited value. This applies particularly to the moderately and severely depressed patient whom one is obliged to admit to hospital. In this patient quick relief of suffering is imperative, and the tendency is to use electroplexy, a treatment of proven value in relieving distress early and with a high degree of success. The results of the present trial and of previous trials (Robin and Harris, 1962; Hutchinson and Smedberg, 1963) show that drugs of this nature do not achieve the immediate success rate of electroplexy. However, our findings suggest that it should be possible to treat many more in-patients successfully if careful selection is employed at certain stages.

Whilst some authors (Fleminger and Groden, 1962), have been unsuccessful in correlating the clinical features with response to treatment, others (Kiloh and Ball, 1962; Hordern *et al.*, 1963) have managed to do so. In comparing factors isolated by Kiloh and Ball with our own findings there is only one (good concentration) common to both studies. A possible explanation for this failure to confirm their findings lies in the fact that the case material of these authors was composed entirely of out-patients.

Our method closely followed that of Hordern and his co-workers. In an item analysis of the Hamilton scale for patients treated with imipramine, they found that severity of 5 of the 17 items was correlated with poor response. These items were: reduction of work and interest, depressed mood, agitation, psychic anxiety and retardation. In our material however only one item on the scale, reduction of work, was significantly associated in its severity with a poor outcome. Hordern and his colleagues do not qualify the term "severity" in terms of actual scoring. We accepted a score of 50 per cent. or more of the possible maximum for each item as indicating severity. Increasing the requirement to 100 per cent. did not enable us to isolate any further items. This is a surprising lack of concordance in studies so similar, and may in part be due to differences in the employment of the rating scale. We have found that practice and discussion were necessary before achieving a satisfactory correlation between our individual scores.

The initial *total* scores on the Hamilton scale in our cases was very definitely associated with outcome. Patients scoring over 50 tended to do badly; only 4 of the 20 patients in this category showed marked improvement after three weeks. Most of the individual items on the scale contributed to the effect (*vide supra*). This result confirms the impression of others (Martin, 1963; Hordern *et al.*, 1963) that severer forms of depression do not do well on drugs of the imipramine type. As Martin points out, however, there are notable exceptions. The patient with the highest score (70) in our series did remarkably well on desipramine.

At the one-week stage we found that the Hamilton scale had great prognostic value. Patients who showed a 50 per cent. improvement, or better, at this point were those most likely to achieve marked improvement after three weeks. Only 3 of the 26 patients showing this degree of improvement failed to respond ultimately, and 7 of the 27 patients scoring badly at this stage went on to full improvement after three weeks. In addition, there was some value in examining the individual items; depressed mood, loss of energy and subjective anxiety tended to improve more markedly in patients eventually responding to the drugs.

We do not feel that too much reliability should be placed on the presenting features of the illness in prescribing these drugs. Certainly, apart from initial severity, no individual symptom constitutes a contra-indication. However our findings suggest that strong reliance should be placed on the degree of response after one week as an indicator of eventual success.

It is interesting that 8 of the 13 patients who

were only moderately improved at three weeks reached the marked improvement category after a further two weeks on drugs. This substantiates the findings of other workers that patients can continue to improve up to five weeks. It also highlights the problem of further management of these patients when three weeks has elapsed without full response. Should they be continued on drugs or given electroplexy? As over 30 per cent. of our patients failed to reach marked improvement with extended treatment it would seem advisable to give electroplexy in addition.

Summary

This study consists of a double-blind trial of desipramine against an established anti-depressant drug, imipramine. It also attempts to devise a rationale for the treatment of hospitalized depressives with these drugs.

The results of the controlled trial show that there is little difference between the two drugs as regards their anti-depressant activity or speed of action. Side-effects also tended to be similar in frequency of occurrence and nature.

Certain items in the clinical presentation have been shown to be correlated with outcome and scoring on the Hamilton scale has been shown to be a particularly useful guide to further management at the end of one week of therapy.

Acknowledgments

We would like to express our thanks to Dr. G. Burnand for help with the statistical calculations; to the Nursing Staff, Psychiatric Social Workers, Pharmacy and Laboratory Staff at Saxondale Hospital and to Geigy Pharmaceuticals Ltd., for generous supplies of the drugs.

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(Received 6 July, 1964)

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BJP 1965, 111:511-516.
Access the most recent version at DOI: 10.1192/bjp.111.475.511